Correspondence

Saliva and the Transmission of Human Herpesvirus 8: Potential Role of Promoter-Arthropod Bites

To the Editor—The study by Mbulaiteye et al. [1] examines the distribution of human herpesvirus 8 (HHV-8) seropositivity within families in rural Tanzania, to determine routes of the infection's spread. Their findings agree with those from epidemiological surveys of other endemic areas; such surveys show that there are significant nonsexual associations within families, with high seroprevalence in young children. Although Mbulaiteye et al. recognize that it is not clear what the routes of HHV-8 transmission are, they propose that young children may become infected with this virus "through exposure to HHV-8–infected saliva, mainly from family members" (p. 1783); concerning the mechanisms of exposure to saliva, Mbulaiteye et al. suggest that it "may occur when mothers premasticate food for infants or clean children's faces with saliva" (p. 1783). Nonetheless, these cultural practices can only partially explain the seroprevalence of HHV-8 in younger children. A more general explanation is provided by Coluzzi et al. [2] and is reinforced by Coluzzi et al. [3], who have suggested that blood-feeding arthropods (e.g., mosquitoes) play a role in the epidemiology of HHV-8 infection.

According to this hypothesis, the conditions for HHV-8 transmission are met when (1) a child shows a response to the bites of blood-feeding arthropods and (2) an HHV-8–seropositive mother (or other relative), attempting to cleanse the spots and to relieve the child's itching and reduce scratching, applies her infective saliva to the bite sites, either by licking or by using her fingers. The habitual use of saliva as first-aid medication is typical in poor villages, such as those in Mbulaiteye et al.'s area of study in Tanzania, but becomes rarer with economic development and progressive improvement in hygiene. Infection may be promoted by a child's scratching the sites of insect bites, and virus replication may be facilitated both by the local down-regulation of immunity and by the recruitment of inflammatory cells induced by arthropod saliva [4–6]. However, we do not suggest that arthropods are directly involved in the transmission of HHV-8; to distinguish between this mode of infection and mechanical or biological vectors, Coluzzi et al. [2] proposed the term "promoter arthropod," to stress the role played in the stimulation of the use of saliva and, possibly, in the facilitation of HHV-8's entry—and subsequent replication—in humans. The promoter-arthropod hypothesis fits well with various and sometimes puzzling epidemiological phenomena—for example, the increase in HHV-8 infection in children >2 years old, who are unlikely to require premasticated food, and the association between HHV-8 and hepatitis B virus [7]. In Mbulaiteye et al.'s study of HHV-8 infection in rural Tanzania [1], the promoter-arthropod hypothesis could explain the higher HHV-8 seroprevalence observed in residents of "low-lying villages" near Lake Victoria, compared with that in residents of "high-elevation villages" (60.1% and 49.7%, respectively; $P = .04$); residents of villages nearer the lake would inevitably suffer higher frequencies of bites from hematophagous arthropods (mostly culicine mosquitoes and ceratopogonid midges [8]) than would the residents of villages on the hills. It follows logically from the promoter-arthropod hypothesis that a more-intense circulation of HHV-8 would be expected in low-lying villages, and it should be feasible to find evidence for such a relationship. After the more-aggressive arthropods are identified (because they are more likely to be the promoter arthropods), villages should be ranked both with regard to the frequency of bites by these arthropods and with regard to the seroprevalence of HHV-8, allowing correlation analysis between the 2 data sets.

Further evidence may be obtained via socioanthropological surveys involving questionnaires (administered to children as well as to adults), to evaluate the frequency of the use of saliva therapy. The results could provide baseline data to be used in an attempt to reduce HHV-8 seroprevalence via behavioral change (i.e., discontinuation of saliva therapy in favor of other treatments for bites) resulting from health-education campaigns in multiple villages; the same health-education campaigns could be conducted in matched control villages, except that they would address various other suitable behavioral changes while carefully avoiding any influence on the use of traditional saliva therapy. The monitoring of seroconversion rates in the 2 groups of villages might demonstrate the validity of the promoter-arthropod hypothesis. Additional, simultaneous serosurveys of infection with hepatitis B and C viruses could provide parallel information on the epidemiologies of these viruses in relation to the use of saliva therapy.

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References

1. Mbulaiteye SM, Pfeiffer RM, Whitby D, Brubaker GR, Shao J, Biggar RJ. Human herpesvirus 8 infection within families in rural Tanzania. J Infect Dis **2003**; 187:1780–5.
2. Coluzzi M, Manno D, Guzzinati S, et al. The bloodsucking arthropod bite as possible cofactor in the transmission of human herpesvirus-8 infection and in the expression of Kaposi's sarcoma disease. Parassitologia **2002**; 44:123–9.
3. Coluzzi M, Calabrò ML, Manno D, Chieco-Bianchi L, Schulz TF, Ascoli V. Reduced seroprevalence of Kaposi's sarcoma–associated herpesvirus (KSHV), human herpesvirus 8 (HHV8), related to suppression of *Anopheles* density in Italy. Med Vet Entomol **2003**; 17:461–4.
4. Ribeiro JM. Blood-feeding arthropods: live syringes or invertebrate pharmacologists? Infect Agents Dis **1995**; 4:143–52.
5. Gillespie RD, Mbow ML, Titus RG. The immunomodulatory factors of bloodfeeding arthropod saliva. Parasite Immunol **2000**; 22:319–31.
6. Kamhawi S. The biological and immunomodulatory properties of sand fly saliva and its role in the establishment of *Leishmania* infection. Microbes Infect **2000**; 2:1765–73.
7. Mayama S, Cuevas LE, Sheldon J, et al. Prevalence and transmission of Kaposi's sarcoma–associated herpesvirus (human herpesvirus 8) in Ugandan children and adolescents. Int J Cancer **1998**; 77:817–20.
8. Smith A. The transmission of filariasis in Ukara Island, Tanganyika. I. A geographical and ecological description of the island with an annotated list of mosquitoes and other arthropods of medical importance. Bull Entomol Res **1955**; 46:419–36.

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Reply

To the Editor—Regarding our recently published paper on intrafamilial transmission of human herpesvirus 8 (HHV-8) within families in rural Tanzania [1], Coluzzi et al. [2] suggest that the "arthropod-promoter" hypothesis [3] may explain, in part, the slightly higher HHV-8 seroprevalence that we observed in residents of low-elevation villages, compared with that in residents of high-elevation villages. Coluzzi et al. hypothesize that HHV-8 is introduced when relatives rub saliva on the insect bites that their children receive and that arthropod saliva may facilitate infection by modifying the local immune responses to HHV-8 [4].

Both Coluzzi et al.'s hypothesis and our own ideas on HHV-8 transmission are based on the premise that HHV-8 is transmitted by saliva [5]. Salivary transmission is supported by data showing that HHV-8 DNA is detected most frequently and at the highest levels in saliva, compared with other body fluids [5], and Epstein-Barr virus (EBV), another γ-herpesvirus, also appears to be transmitted by saliva. However, there remains uncertainty about the validity of this concept. We are puzzled as to why, if saliva is in fact the body fluid dominant in HHV-8 transmission, the prevalence in populations is so variable by age, by geography, and by exposure group [6]. African children appear to become infected with HHV-8 well after infancy, and yet, because of maternal premastication of supplement foods, salivary exposure is most common in early childhood [2]. Furthermore, the limited geographic distribution of HHV-8 contrasts with the more-ubiquitous geographic distribution of the similarly transmitted EBV [7]. Also, in Western nations, among HIV-negative persons, the prevalence of HHV-8 is much higher in homosexual men [8] than in heterosexual persons [6], even though both groups regularly engage in kissing with saliva exchange, and there does not appear to be a major increase in prevalence in heterosexual adolescents, in whom kissing is most frequent. Is this simply a question of variation between the viral levels and infectiousness of EBV and those of HHV-8, or do these differences arise because of specific saliva-sharing practices and/or because cofactors are required to facilitate HHV-8 transmission by saliva?

Coluzzi et al. have suggested a role for arthropods. However, we do not know whether the bite frequency of arthropods varies with village elevation. Given that this association is ecological, we urge caution, because such potential confounders as water access, intestinal helminths, socioeconomic status, and many others that correlate with residence cannot be excluded. Moreover, in African societies, saliva also is frequently used for facial cleaning and in ritual application, in addition to medical treatment and infant and early-childhood feeding [9]. We cannot determine the relative contributions of any of these means of salivary exposure in HHV-8 transmission. Finally, is it possible that 1 or more of the diseases transmitted by arthropods are the cofactors, not the proteins in the saliva of arthropods?

We believe that the broader question that is implicitly raised by the arthropod-promoter hypothesis is whether (and, if so, which) cofactors are at play in different populations during salivary transmission of HHV-8. In light of the seroepidemiology of HHV-8, such cofactors should be frequent in Africa but infrequent in northern Europe, the United States, and Asia. The cofactors that are implied in the arthropod-promoter hypothesis would not readily explain the higher risks for HHV-8 infection in homosexual men in Western countries. Thus, whereas we continue to think that saliva is likely the vehicle for HHV-8 transmission, we endorse the premise that there may be additional cofactors that determine the success and extent of HHV-8 transmission by this route. The identification of these cofactors could provide a sound basis for the development of interventions for the prevention of HHV-8 transmission.

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References

1. Mbulaiteye SM, Pfeiffer RM, Whitby D, Brubaker GR, Shao J, Biggar RJ. Human herpesvirus 8 infection within families in rural Tanzania. J Infect Dis **2003**; 187:1780–5.
2. Coluzzi M, Calabrò ML, Manno D, et al. Saliva and the transmission of human herpesvirus 8: potential role of promoter-arthropod bites. J Infect Dis **2004**; 190:199–200 (in this issue).
3. Coluzzi M, Manno D, Guzzinati S, et al. The bloodsucking arthropod bite as possible cofactor in the transmission of human herpesvirus–8

infection and in the expression of Kaposi's sarcoma disease. Parassitologia **2002**; 44:123–9.
4. Gillespie RD, Mbow ML, Titus RG. The immunomodulatory factors of bloodfeeding arthropod saliva. Parasite Immunol **2000**; 22:319–31.
5. Corey L, Brodie S, Huang ML, Koelle DM, Wald A. HHV-8 infection: a model for reactivation and transmission. Rev Med Virol **2002**; 12:47–63.
6. Martin JN. Diagnosis and epidemiology of human herpesvirus 8 infection. Semin Hematol **2003**; 40:133–42.
7. Macsween KF, Crawford DH. Epstein-Barr virus: recent advances. Lancet Infect Dis **2003**; 3: 131–40.
8. Pauk J, Huang ML, Brodie SJ, et al. Mucosal shedding of human herpesvirus 8 in men. N Engl J Med **2000**; 343:1369–77.
9. Wojcicki JM. Traditional behavioural practices, the exchange of saliva and HHV-8 transmission in sub-Saharan African populations. Br J Cancer **2003**; 89:2016–7.

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